Impacts of ABPM Quality Criteria on Primary Endpoint, the Comparison of Two ABPM Parameter Derivation Methods and ABPM Missing Data Imputation

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Abstract

In May 2018, the Food and Drug Administration (FDA) released a new draft guidance — "Assessment of Pressor Effects of Drugs Guidance for Industry". The purpose of the guidance is to advise sponsors on the premarketing assessment of a drug's effect on blood pressure. As elevated blood pressure is known to increase the risk of stroke, heart attack, and death, the effect of a drug on blood pressure can be an important consideration in cardiovascular safety profiling and benefit-risk assessment.

Ambulatory blood pressure monitoring (ABPM) study is recommended in the guidance for the premarketing assessment of a drug's presser effect. To facilitate the successful implementation of this guidance, we investigated the impacts of different ABPM quality criteria on the primary analysis and two commonly used methods in the derivation of ABPM parameters. ABPM data features and missingness were investigated as well.

Introduction

ABPM is when blood pressure is measured up to 24 hours while a subject is moving around and living a normal daily life. The review of ABPM study was designated to QT-IRT by CDER and thus the team was renamed to CSS-IRT in 2019.

There are many criteria for ABPM quality control. Each criterion comprises a set of conditions, such as pre-defining a valid measurement and a valid hour; specifying the ranges of daytime and nighttime hours; setting minimum number of valid measurements required for a daytime or nighttime hour, maximum number of (consecutive) missing hours allowed in 24 hours, daytime, and nighttime, and required minimum percentage of expected total measurements, etc.

We evaluated the ABPM primary endpoint — mean change from baseline in systolic blood pressure (SBP), and other ABPM parameters using 21 different criteria. The first 7 of them are: Precision, IRT-2, EU-1, EU-2, Parati (2014), Synergy, and New[1].

- **Precision Trial**: no more than 3 consecutive hours are missing, or more than 5 hours in total are missing. Any hour with a valid reading is counted as a valid hour; hours with no valid reading were considered as "missing" hours.
- **IRT-2**: 24-hour recording with at least 50% of expected measurements when using a 24-hour average metric.
- **EU-1**: 24-hour recording with at least 70% of expected measurements, at least 20 valid awake [09:00 to 20:59 clock hr] measurements, and at least 7 valid asleep [01:00 to 05:59 clock hr] measurements.

Introduction Continuation

For other criteria, specifications and conditions vary and the definition sets mostly involve change in required number of valid measurements during a time range, change in required percentage of expected measurements, or a combination of both. Due to limited space, more criteria details will be skipped[1].

Materials and Methods

Figure 1 and 2 display a typical ABPM device and the wearing of it during daytime and nighttime. As ambulatory blood pressure (ABP) is collected continuously during a 24-hour period, and as it's through an automatic digital device, quality control is very important since 1 ~ 3 mm Hg variation in BP is of concern, especially for drugs indicated for chronic use.

Data from a large randomized ABPM trial (N=543) were used for the investigation. The study is a Phase IV parallel group study to evaluate the pressor effect of three active drugs. ABP was collected at baseline, month 2 (Visit 4) and month 4 (Visit 5). At each visit, the Precision criterion was applied to 24-hour ABP, if a visit failed the criterion, a re-visit was scheduled in the study. For non-completers, month 2 data were carried over (LOCF) for primary analysis, but non-LOCF data and many secondary endpoints were all of interests and investigated.

Figure 1. A typical ABPM device

Figure 2. 24-hour ABPM measuring

Criterion algorithms, especially procedures tackling missing and consecutive missing hours, were developed based on raw replicate data at each subject's visit level. The algorithms were utilized to check whether a visit meet the requirements of a specific criterion. In case both scheduled visit and re-visit were qualified for a new criterion, the re-visit was chosen for analysis. Cases of double-qualifying are infrequent for all new criteria as revisits only account for a small percentage of all visits in original data.

After criterion qualified valid visits were selected, two methods of deriving ABPM parameters were utilized: arithmetic means over raw data and means of hourly means. According to Michael Frank et al., the later one was used by most ABPM devices and softwares. Comparisons of SBP and change from baseline in SBP based on different criteria and based on different deriving methods were made, both by descriptive statistics and by modeling to assess treatment effects.

Results and Discussion

As many tables and figures can't be displayed due to limited space, a few selected figures from the pool of analysis results are displayed below (all visit 5: without last observation carried forward (LOCF)).

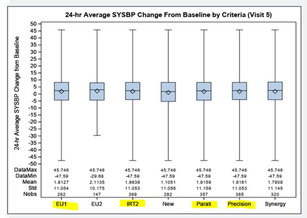

Figure 3. 24-hour average SYSBP change from baseline at Month 4 by criteria

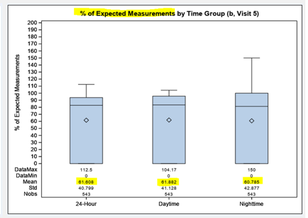

Figure 4. Percentage of expected measurements by time group and visit

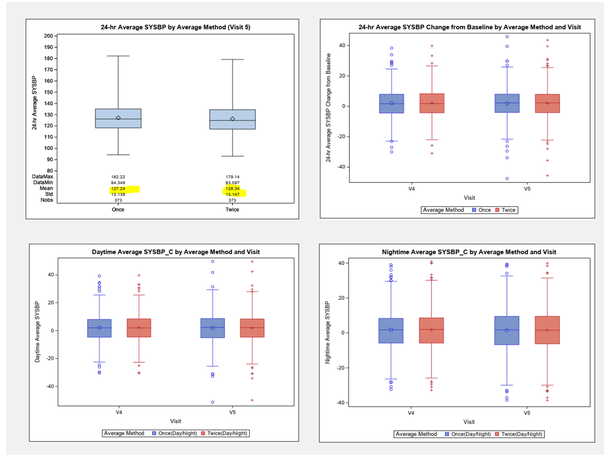

Figure 5. Comparisons of differences between two ABPM derivation methods

Conclusions

Our analyses showed that the selected study collected high quality ABPM data. Results and conclusions from different criteria may change if assessments were evaluated using moderate or low-quality ABPM data.

- Too stringent criteria will reduce # of subjects with valid ABPM values but may not improve the variability/accuracy in estimating the mean BP.
- Three criteria, including criterion IRT-2, work well in general.
- The % of expected ABPM readings decreased across baseline visit, interim visit, and final visit. Some sensitivity analyses may need to access the robustness of the primary analysis results based on 24-hr mean SBP.
- The mean of 24-hr mean SBP based on arithmetic mean (average once) tended to be higher than that derived from hourly mean (average twice). The magnitude of the difference is around 1 mm Hg. The mean of daytime and nighttime mean SBP is similar between average once and average twice.
- The above findings are consistent with results from literatures. Significant differences exist between the two methods even in high quality data.
- The variability of 24-hr, daytime, and nighttime mean SBP is similar between average once and average twice.
- The mean of change from baseline in 24-hr, daytime, and nighttime mean SBP is similar between average once and average twice.

We made recommendations of ABPM qualification criterion based on the 21 ABPM criteria investigated. We presented that there are differences in the ABPM values based on different derivation methods.

ABPM studies collect blood pressure data repeatedly in each hour over a 24-hour time range, which inevitably brings missing data issue. As normally these studies monitor subjects over a long period of time, another level of missing — missing visit — is also inevitable. Missing hours and missing visits, especially at nighttime and later phase of a trial, are common in ABPM study. Data obtained from ABPM studies offered us quick and ready resources for missing data research.

ABPM data missing pattern, missing mechanism, missing imputation , and analysis were studied for the selected study. We showed that different imputation methods as sensitivity analysis will provide different results and it is important to pre-specify sensitivity analysis to access the robustness of primary analysis due to missing data in ABPM studies. As more effort will be input to this area, we'll summarize missing data results at later time.

Acknowledgements and Contact

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[1]For further information, please contact

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